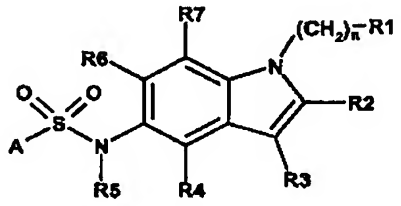
REMARKS

Claims 1-14, 18, 19, 46, 47, and 74-93 are pending in the present application.

The claimed invention is drawn to a sulfonamide compound of general formula (Ia)



(Ia)

wherein

R^1 represents an $-NR^8R^9$ radical or a saturated or unsaturated, optionally at least mono-substituted, cycloaliphatic radical, which may optionally contain at least one heteroatom as a ring member and/or which may be condensed with a saturated or unsaturated, optionally at least mono-substituted mono- or bicyclic cycloaliphatic ring system, which may optionally contain at least one heteroatom as a ring member,

R^2, R^3, R^4, R^6 and R^7, identical or different, each represent hydrogen, halogen, nitro, alkoxy, cyano, a saturated or unsaturated, linear or branched, optionally at least mono-substituted aliphatic radical or an optionally at least mono-substituted phenyl radical or an optionally at least mono-substituted heteroaryl radical,

R^5 represents hydrogen or a saturated or unsaturated, linear or branched, optionally at least mono-substituted aliphatic radical,

R^8 and R^9, identical or different, each represent hydrogen or a saturated or unsaturated, linear or branched, optionally at least mono-substituted aliphatic radical,

with the proviso that R^8 and R^9 are not hydrogen at the same time, and if one of them, R^8 and R^9, represents a saturated or unsaturated, linear or branched, optionally at least mono-substituted C_1-C_4 aliphatic radical, the other one represents a saturated or unsaturated, linear or branched, optionally at least mono-substituted aliphatic radical with at least five carbon atoms, or

R^8 and R^9 together with the bridging nitrogen atom form a saturated or unsaturated, optionally at least mono-substituted heterocyclic ring, which may contain at least one additional heteroatom as a ring member and/or which may be condensed with a saturated or unsaturated, optionally at least mono-substituted, mono- or bicyclic cycloaliphatic ring system which may optionally contain at least one heteroatom as a ring member,

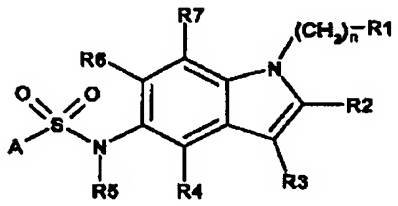
A represents an optionally at least mono-substituted mono- or polycyclic aromatic ring system, which may be bonded via an optionally at least mono-substituted alkylene, alkenylene or alkynylene group and/or which may contain at least one heteroatom as a ring member in one or more of its rings,

and

n is 0, 1, 2, 3 or 4;

optionally in form of one of its stereoisomers, its racemate or in form of a mixture of at least two of its stereoisomers, in any mixing ratio, or a salt thereof. (See Claim 1, Claims 2-8, 18, 19, 74-83, and 92 depend from Claim 1 either directly or indirectly).

The present invention also provides a sulfonamide compound of general formula (Ib)



(Ib)

wherein

R^1 represents a $-NR^8R^9$ radical,

R^2, R^3, R^4, R^6 and R^7, identical or different, each represent hydrogen, halogen, nitro, alkoxy, cyano, a saturated or unsaturated, optionally at least mono-substituted, linear or branched aliphatic radical, or an optionally at least mono-substituted phenyl or an optionally at least mono-substituted heteroaryl radical,

R^5 represents hydrogen or a saturated or unsaturated, linear or branched, optionally at least mono-substituted aliphatic radical,

R^8 and R^9, identical or different, each represent hydrogen or a saturated or unsaturated, linear or branched, optionally at least mono-substituted, C_1-C_4 aliphatic radical,

A represents an optionally at least mono-substituted mono- or polycyclic aromatic ring system, which may be bonded via an optionally at least mono-substituted alkylene, alkenylene or alkynylene group and/or which may contain at least one heteroatom as a ring member in one or more of its rings,

and n is 0, 1, 2, 3 or 4;

optionally in form of one of its stereoisomers its racemate or in form of a mixture of at least two of its stereoisomers, in any mixing ratio, or a salt thereof. (See Claim 9, Claims 10-14, 46, 47, 84-91, and 93 depend from Claim 9 either directly or indirectly).

Claims 1-14, 18-19, 46-47 and 74-93 stand rejected under 35 U.S.C. §103(a) as being obvious over Merce-Vidal et al (WO 03/042175; English equivalent taken as CA 2466965) in view of Filla et al (WO 02/060871). This rejection is respectfully traversed.

Despite previous Applicants' arguments, the Examiner maintains in the Final Office Action mailed October 1, 2009, as well as the Examiner's Answer mailed November 5, 2010, that the compounds of the present invention differs from the prior art compounds taught by Merce-Vidal et al by a single modification (i.e., is a positional isomer, compounds which *In re Wilder*, 563 F.2d 457 (CCPA 1977) teach are generally of sufficiently close structural similarity to possess similar properties) and that said single modification would have also been *prima facie* obvious in view of Filla et al. Applicants disagree for the reasons that follow:

As discussed in the response filed by the Applicants on August 21, 2009 and the Appeal Brief filed on August 4, 2010, the Court of Appeals for the Federal Circuit clearly state in *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) that in order to find a *prima facie* case of unpatentability, a showing that the ***"prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention"*** was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound***. (emphasis added)

Applicants assert that the **Examiner's arguments appearing in the Final Office Action are not proper to establish a *prima facie* obviousness rejection.** In this regard, instead of showing the above-mentioned requisite reason, the Final Office Action is mainly aimed to differentiate the instant case from *Takeda*.

Applicants concede that the present case is not *completely* equivalent to *Takeda*. *Takeda* is cited as a relatively recent case which assesses the patentability between positional isomers and provides fundamental points of law to establish a *prima facie* case of obviousness in this context, such as the requirement of some suggestion in the prior art to make the ***specific*** molecular modifications necessary to make the claimed invention. While such basic points of law should apply to the instant situation, the Examiner should not take the deviations of the present case with respect to *Takeda* as an immediate symptom of obviousness.

In view of the foregoing, Applicants submit that the present invention is not obvious in view of Merce-Vidal et al or Filla et al as these references fail to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the

manner necessary to arrive at the claimed compounds. Thus, Merce-Vidal et al and Filla et al fail to support even a *prima facie* case of obviousness.

Furthermore, the Examiner is reminded that for a claimed invention to be obvious, the possible modifications of the prior art must be finite. *See*, *Rolls-Royce PLC v. United Technologies Corp.*, 95 USPQ2d 1097 (Fed. Cir. 2010). As stated by the Federal Circuit:

> ***To determine that an invention would have been obvious*** to try on the basis of the record before the time of invention, ***this court has clarified***, with respect to inventions requiring selection of a species from a disclosed genus, ***that the possible approaches and selection to solve the problem must be*** "known and ***finite.***" *See Abbott*, 544 F.3d at 1351 (holding as conditions in which "obvious to try" may negate patentability, "the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option"). . . . In this case, the broad selection of choices for further investigation available to a person of ordinary skill included any degree of sweep. *See Takeda*, 492 F.3d at 1359 (holding the invention not obvious to try because the prior art disclosed a broad selection of compounds that an ordinarily skilled artisan could have selected for further investigation).
>
> Rolls-Royce, at 1107, emphasis added.

This case is like that in *Rolls-Royce* in that there are countless possible theoretical modifications of the prior art with no teaching that any one modification should be selected. Indeed, the artisan could readily modify any and every position on the compound disclosed by Merce-Vidal et al, not just the single position identified by the Examiner. The lack of guidance for the starting compound and the lack of suggestion of how to modify the compound is precisely why *Takeda* was decided the way it was. Just like in the *Takeda* and *Rolls-Royce*, the artisan would have no reasonable basis of where to start and how to arrive at the compounds as claimed.

Moreover, in *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.* (Fed. Cir. 2009), the Federal Circuit articulated a 3 element test for a *prima facie* case of obviousness based on structural similarity of a lead compound to a claimed compound as requiring: (1) a

preliminary finding that one of ordinary skill...would have selected [the prior art compound] as a lead compound; (2) a person of ordinary skill must have reason to attempt to make the claimed compound by modifying the lead compound; and (3) a reasonable expectation of success in making the claimed compound by modifying the lead compound.

There is no disclosure in Merce-Vidal et al or Filla et al to select the specific compound alleged as a starting point, nor is there a suggestion that one should use this compound to arrive at the claimed invention. Additionally, there is no suggestion that the modification would provide a compound giving the properties of the claimed compounds with a reasonable expectation of success.

From the Office's own *2010 KSR Guidelines Update*, citing *Procter & Gamble*, even "where there was reason to select and modify the lead compound to obtain the claimed compound, but no reasonable expectation of success, the claimed compound would not have been obvious." 75 FR 53643, at 53652.

At best, based on the combined disclosures of Merce-Vidal et al and Filla et al, the Examiner may allege that the artisan would possess a general ability to pick-and-choose limitations to arrive at a composition that overlaps with the claimed compositions. However, this treatment are nothing more that an *ex post facto* analysis using Applicants' disclosure as a guidepost to piece together seemingly disparate disclosures. Indeed, the Examiner's alleged case of obviousness is nothing more than "*a posteriori*" argumentation which is largely based on Applicants' invention rather than the state of the art existing at the time of their invention. The Examiner is reminded that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art" (MPEP 2142; see also MPEP 2145(X)(A)).

Even if it is the Examiner's position that modifications in the cited references would have been within the general abilities of the skilled artisan, a statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). At best, the combined disclosures could be taken as an "invitation to experiment" or could be viewed as providing an "obvious to try" argument. However, "obvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680 81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 [82 USPQ2d 1385](2007) does not eliminate the "obvious to try is not obvious" standard, as it clearly states that "obvious to try" may constitute obviousness, but only under certain circumstances. Specifically, KSR stated that the fact that a claimed combination of elements was "obvious to try" might show that such combination was obvious under 35 U.S.C. § 103, since, if there is design need or market pressure to solve the problem, and there are finite number of identified, predictable solutions, person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation.

Applicants respectfully submit that the Examiner has not offered any evidence that there is a recognized "design need or market pressure to solve the problem". Indeed, the

cited references make no suggestion that such a need even exists. Further, the Examiner fails to show that there are a "finite number of identified, predictable solutions". In fact, there is nearly an infinite number of ways that the references may be combined with respect to the various components and concentrations disclosed therein. The Examiner also does not provide any evidence that a "person of ordinary skill in art has good reason to pursue known options within his or her technical grasp". It is clear from the references themselves that the artisan had no such reason to modify the various disclosures to arrive at the claimed invention. All that the Examiner appears to provide is that selection of the starting compound and the modifications to arrive at the claimed invention may be within the general abilities of the skilled artisan, but again this is not the proper standard for obviousness (*Ex parte Levengood*).

Indeed, absent Applicants disclosure to serve as the guidepost, no objective reason to combine the teachings in a way that would place the artisan in possession of the claimed invention can be found. The Examiner merely attempts to use the present application to impermissibly piece together random tidbits of information from separate and disparate references to show that all aspects of the claimed invention were individually known in the art and alleges that this would, in and of itself, provide a basis to modify the disclosures of the cited art.

Tryptamine-like structure

Despite the foregoing, and putting aside the foregoing legal precedent that clearly shows that the foregoing obviousness rejections are without merit, the Examiner contends that the present case is distinguishable from *Takeda*. In this regard, the Examiner alleges that the selected compound taught by Merce-Vidal et al differs from the presently claimed

compound in only **one** respect (i.e., ring walking the moiety from position 3 to position 1) whereas in *Takeda* the compounds differed in **two** respects (i.e., ring walking and homologation).

Furthermore, even assuming that the "ring walking" encompasses two changes (i.e. "the introduction ... at position 1" and "the elimination ... at position 3" of the substituent (Applicant Arguments filed August 21, 2009), the Examiner contends that the present case would be still distinguishable from *Takeda* in that the prior art compound taught by Merce-Vidal et al differs from the instantly claimed compound in only **two** respect (i.e., ring walking the moiety from position 3 to position 1 – which involves two changes) whereas in *Takeda* the compounds differed in **three** respects (i.e., ring walking, which involves two changes, and homologation).

Further, asserted claim 1 of the '777 patent in Takeda recites a formula general wherein the ethyl-substituted pyridyl ring is located at one of four available positions on the pyridyl ring, generating 3-, 4-, 5- and 6-ethyl compounds. Accordingly, the court allowed claim 1 in spite of the 6-ethylpyridyl derivative would differ from the prior art compound b in only **one** respect (homologation) [compound b possesses a pyridyl ring in which a methyl (CH3) group is attached to the 6-position].

Regardless of the specific number of differences in the present case as compared to Takeda, the point at issue is that Merce-Vidal et al provides no hint as to moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring without losing affinity for the 5-HT_6 receptor. Neither would the skilled person have been motivated to change the -$(CH_2)_n$-R^2 moiety of Merce-Vidal et al to position 1 in view of the teaching of Filla et al, since *inter alia* as deeply discussed during the examination and additionally dealt

with hereinafter in section "*Combination of Merce-Vidal and Filla*", the substituent at position 1 in Filla et al is not an aminoalkyl radical as requires the instant invention.

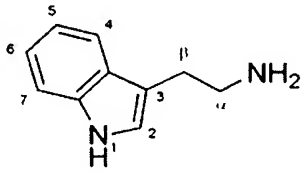
Moreover, as discussed previously, in the present case it is of the utmost importance to identify that the change of the substituent of the compounds disclosed in Merce-Vidal et al from position 3 to position 1 ("ring walking") in order to arrive at the claimed compounds involves two changes as the second one disrupts the so characteristic tryptamine-like structure. In concrete, said ring walking comprises the following modifications:

- the introduction of a precisely defined substituent containing nitrogen at position 1;
- but also, and very importantly, the elimination of this specific and mandatory substituent from position 3 in Merce-Vidal et al.

With respect to the first change, Applicants submit that it would not be obvious that the introduction of an aminoalkyl substituent at position 1 would give compounds with 5-HT_6 activity. As already pointed out in previous responses, Filla et al do not show a single example of the biological activity of the indole compounds described therein (see also section "*Unexpectedly superior properties over the prior art*" hereinafter). Further, the substituent at position 1 in Filla et al is not an aminoalkyl as defined in the instantly claimed compounds. Thus, the skilled artisan would find not reasonable motivation or expectation of success in either Filla et al and/or Merce-Vidal et al to introduce a alkylamino substituent at position 1 of the indole ring.

Concerning the second change, Applicants submit that the skilled artisan would not consider that the elimination of the specific substituent at position 3 in the compounds of Merce-Vidal et al could give compounds with 5-HT_6 activity.

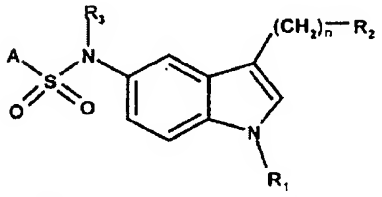
In this regard, Applicants again emphasize the "tryptamine-like" argument as, in contrast to the indole compounds disclosed in Merce-Vidal et al and Filla et al, the compounds of the present invention do not have a tryptamine-like structure.



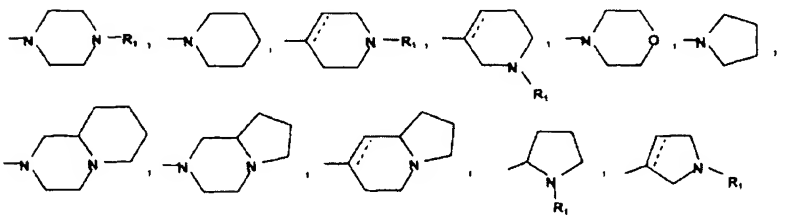
tryptamine

As may be observe, the general formulae described both in Merce-Vidal et al and in Filla et al are 2-aminoalkyindoles:

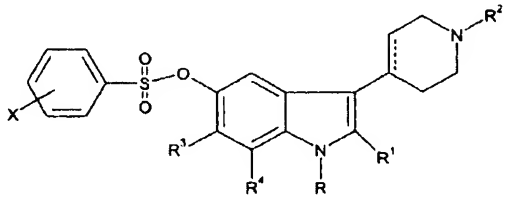
Merce-Vidal et al.



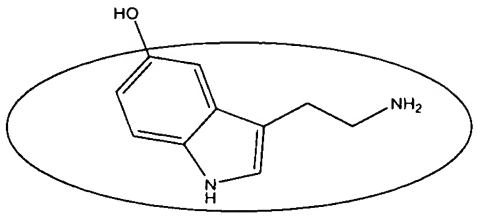
R_2 represents $-NR_4R_5$ or a group with formula:



Filla et al.



Applicants have previously submitted appropriate evidence of that i) the compounds disclosed in the cited references are based on a tryptamine framework and ii) it is widely known in the state of the art that said tryptamine framework is common in numerous serotonin receptor ligands. Indeed, serotonin (5-hydroxytryptamine) presents the following structure:

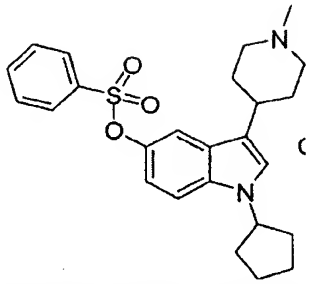


As stated for instance in Sophie-Isabelle Bascop et al., *Arkivoc* **2003** 46-61, 2(3)-aminoalkyl indoles, not only tryptamine derivatives but also homotryptamine and isotryptamine related derivatives, have attracted considerable interest as potent and selective serotonin receptor ligands, such as 5-HT_6 receptor. Some documents reporting this structure-activity relationship are shown hereinunder:

- "2-Substituted Tryptamines: Agents with Selectivity for 5-HT6 Serotonin Receptors", Richard A. Glennon et al., *J. Med. Chem.*, **2000**, *43* (5), pp 1011–1018
- "N1-(Benzenesulfonyl)tryptamines as novel 5-HT6 antagonists", Yuching Tsai et al., *Bioorganic & medicinal chemistry letters* **2000**, vol. 10, no 20, pp. 2295-2299
- "5-halo-tryptamine derivatives used as ligands on the 5-HT6 and/or 5-HT7 serotonin receptors", US 7098233

Therefore, in the present case a person of ordinary skill in the art would not have found apparent to move the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring as discussed above because such movement would *involve the rupture of the tryptamine-like structure*, which was considered essential for the activity as shown in Merce-Vidal et al and in Filla et al.

However, and surprisingly, the Examiner maintains that Example 28 in Filla et al (page 67) does not appear to show a trytamine-like structure since it possesses a 3-aminocycloalkylindole structure (i.e. a tertiary amine), but not a 3-aminoalkylindole basic structure (i.e. a primary amine).



Example 28, Filla et al

Applicants disagree and respectfully state that **the tryptamine structure is clearly present in Example 28 of Filla et al**, as may be appreciate from just the prior art references cited above. It is to be noted in this respect for instance that compounds 6-16 disclosed in Glennon et al (*Journal of Medicinal Chemistry*, 2000, Vol. 43, No. 5), or compounds 5-16 disclosed in Tsai et al (*Bioorganic & medicinal chemistry letters* **2000**, vol. 10, no 20, pp. 2295-2299) in spite of being tertiary amines, are considered as tryptamine analogues.

In the Examiner's answer, the Examiner appears to confuse the issue of "tryptamine-like" and "tryptamine analogues". The Examiner suggests at page 15 of the Examiner's Answer that "tryptamine analogues" is considered significantly broader than the genus of compounds encompassed by "tryptamine-like." However, the Examiner offers no support for this position and does not account for how, even if true, this position would support his alleged obviousness case. For the reasons given above, Applicants submit that the tryptamine structure is clearly present in Example 28 of Filla et al.

Routine drug optimization process

In the Final Office Action mailed October 1, 2009, the Examiner also contends that Applicants have not provide evidence to suggest that the ring walking was not a routine step in the drug optimization process at the time the instant invention was made (as was the case in *Takeda*; see page 1360).

Again, it is recalled that the point at issue here is not how the present application differs from *Takeda* but the legal principles provided in *Takeda* to establish a *prima facie* case of obviousness when assessing the patentability between positional isomers. Hence, Applicants state according to *Takeda* the concept of "routine steps in the drug optimization process" must be associated with the existence of any motivation in the prior art to make the specific molecular modifications to the compounds disclosed in the prior art that are necessary to achieve the claimed compounds. Therefore, the change of the substituent of the compounds disclosed in Merce-Vidal et al from position 3 to position 1 ("ring walking") does not represent a routine step in the drug optimization process since there is nothing in the prior art to suggest performing said ring walking.

Combination of Merce-Vidal and Filla

Further, the Examiner contends that the specific molecular modifications necessary to achieve the claimed invention are motivated in further view of Filla et al.

As has been widely discussed, the disclosure of Filla et al does not provide any basis to motivate the skilled person to change the $-(CH_2)_n-R^2$ moiety of Merce-Vidal et al to position 1 of the indole ring, much less generate a reasonable expectation of success as alleged by the Examiner.

The Examiner's attention is first drawn to the fact that position 3 on the indole ring in Merce-Vidal et al is substituted by a $-(CH_2)_n-R^2$ moiety, wherein R^2 represents $-NR^4R^5$ or a specific non-aromatic nitrogen containing ring selected from a list of 11 different chemical formulae. On the contrary, position 1 on the indole in Filla et al does not contain the possibility of an amino-alkyl chain nor a non-aromatic nitrogen containing ring. Further, position 5 on the compounds of Filla et al in comparison with Merce-Vidal et al is occupied

by a different chemical group (sulfonic acid vs sulfonamide). Accordingly, both Merce-Vidal et al and Filla et al disclose indole compounds differing not only in the position of their substituents, but also in their nature.

Therefore, the skilled artisan, starting from Merce-Vidal et al would not have any basis and/or motivation to change the $-(CH_2)_n-R^2$ moiety to position 1, because this implies going beyond the teaching of both Merce-Vidal et al and Filla et al, as well as ignoring the recommendations of Filla et al for the specific substituents that are to be used at position 1 in order to obtain compounds which are antagonists of the 5-HT_6 receptor. The definition of R in Filla et al is

> *"R is hydrogen, Cl-C6 alkyl, substituted Cl-C6 alkyl, C3-C6 cycloalkyl, C1-C6 alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl, naphthylsulfonyl, benzylsulfonyl, or substituted benzylsulfonyl;"*

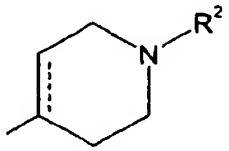
According to Filla et al (page 11, lines 31-37) preferred antagonists of 5-HT_6 receptor are compounds of formula I wherein **R** is hydrogen or C_1-C_6 alkyl, R and R^1 are taken together to form $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$, or R and R^4 are taken together to form $-CH_2-CH_2-CH_2-$.

From the foregoing, it is clear that the substituent R at position 1 on the indole in Filla et al does not include the groups disclosed in Merce-Vidal et al for position 3.

Thus, in the unlikely event that the skilled artisan would consider modifying the compounds of Merce-Vidal et al in order to introduce a substituent at position 1 on the nitrogen atom of the indole ring, which is a very specific position, he would always consider the substituents proposed by Filla et al for this position, and no others. There is no reason to ignore the substituents proposed by Filla et al, and take instead the substituent that is at position 3 in Merce-Vidal et al.

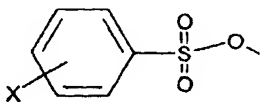
It is also important to note that the substituents of a chemical compound may not be interpreted in isolation. In the present case, the general formula of the indole derivatives disclosed in Filla et al have two additional substitutions clearly unrelated to the compounds of the present invention, namely:

- Position 3 of the indole derivatives of the present invention does not allow an heterocyclic moiety other than an heteroaryl radical, which implies aromaticity. On the contrary, in Filla et al the moiety



is mandatory in position 3 of the indole ring, as stated in the general formula (I) of said application.

- Position 5 of the indol-5-yl sulfonamide derivatives of the present invention is always substituted by a sulfonamide moiety, whereas said position is necessary substituted by a sulfonic acid moiety in Filla et al, as stated in the general formula (I) of the application, concretely by the following moiety



The Examiner is respectfully reminded that he is not allowed to cherry-pick limitations for the combination of Filla et al with Merce-Vidal et al in an attempt to establish a *prima facie* case of obviousness. Specifically:

> The "as a whole" instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. Ruiz v. A.B. Chance Co., 69 U.S.P.Q.2d 1686, 1690 (Fed. Cir. 2004).

It is notorious that Filla et al does not suggest making over Merce-Vidal et al the ***specific molecular modifications*** necessary to achieve the claimed invention, as required to find a *prima facie* case of unpatentability (*Takeda*).

Unexpectedly superior properties over the prior art

Further, the Examiner contends that there is nothing in record to indicate that the instantly claimed compound possesses any unexpectedly superior properties over the prior art compound taught by Merce-Vidal et al such as, for example, reduced toxicity (as in *Takeda*) to overcome this *prima facie* rejection.

Applicants newly state that before comparing the properties of the claimed and the prior art compounds, the *prima facie* rejection requires finding in the prior art any reason that would have led a skilled artisan to modify the compounds disclosed in Merce-Vidal et al in the manner necessary to arrive at the claimed compounds.

Merce-Vidal et al, taken alone, fails to provide any hint to move the amino moiety or the *N*-containing cycloaliphatic ring to the 1-position of the indole ring without losing affinity for the 5-HT_6 receptor. Filla et al does not suggest to change the -$(CH_2)_n$-R^2 moiety of Merce-Vidal et al to position 1 either.

Further, it should be noted that Filla et al contains several synthetic examples and tests which can be carried out to evaluate the compounds disclosed therein but no concrete result to these tests of at least one compound. Accordingly, it is doubtful that the skilled artisan from Filla et al would consider ring-walking the moiety to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT6 modulators.

Positional isomers

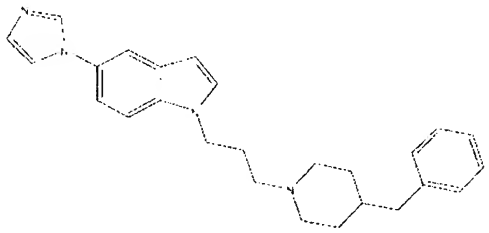
The shift of $-(CH_2)_n-R^1$ from position 3 on the indole ring (as in Merce-Vidal et al) to position 1 on the indole ring (as in the instant application) is not irrelevant. Examiner's attention is drawn to MPEP 2144.09 which states:

> "*Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are* ***generally*** *of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder 563 F.2d 457, 195 USPQ 426 (CCPA 1977).*" (emphasis added)
>
> ***"Isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other.*** Ex parte Mowry, 91 USPQ 219 (Bd. App. 1950) (claimed cyclohexylstyrene not prima facie obvious over prior art isohexylstyrene)." (emphasis added)

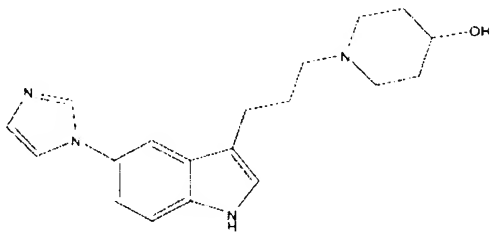
Thus, even it were the case that the claimed compounds are simply position isomers or homologs of the compounds disclosed by Merce-Vidal et al Applicants, who would bear the burden of proof, have provided bibliographic evidences in the response filed on November 28, 2008 to prove that the different biological properties between 1-substituted and 3-substituted indoles are known from the prior art. The documents provided (WO 9320065 vs Russell, M.G.; *J. Med. Chem.*; (**1999**); 42(24); 4981-5001; Liou, J.P.; *J. Med. Chem.*; (**2007**); 50(18); 4548-4552 vs Leonard, B.E.; *Neuropharmacology*; (**1972**); 11(3); 373-384) show how such positional isomers not only can have a different activity regarding the same receptor, but also their activity can be associated with different receptors, which implies totally different medical uses.

Specifically, Merce-Vidal et al provides no hint as to moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring without losing affinity for the 5-HT_6 receptor.

In addition, the Examiner's assertions do not stand comparison with similar situations described in the state of the art. For example, compound (1) is claimed as inhibitor of thromboxane A2 synthesis in WO 9320065, while compound (2), having a similar substituent but in position 3, is described as highly selective h5-HT1D receptor agonist in Russell, M.G.; *J. Med. Chem.*; (**1999**); 42(24); 4981-5001.

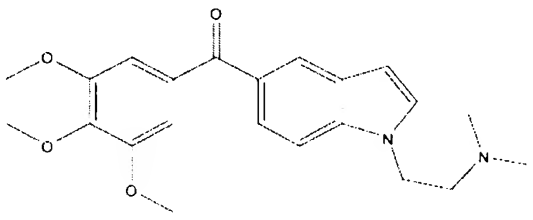


Compound (1)

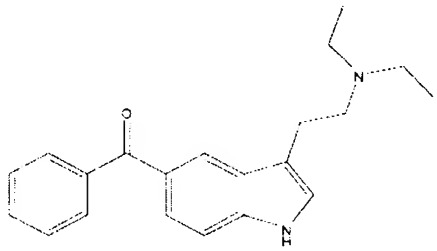


Compound (2)

A similar situation arises when comparing compound (5), which is described as potent antitubulin agent in Liou, J.P.; *J. Med. Chem.*; (**2007**); 50(18); 4548-4552, with compound (6) of Leonard, B.E.; *Neuropharmacology*; (**1972**); 11(3); 373-384, which is described as having effects on brain monoamines and their precursor amino acids.



Compound (5)

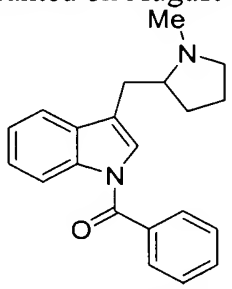


Compound (6)

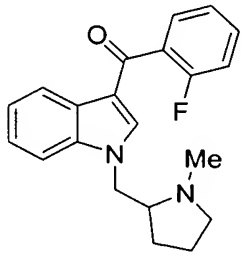
Thus, the skilled artisan considering Merce-Vidal et al in light of the prior art, could expect changing the $-(CH_2)_n-R^2$ moiety to position 1 to have dramatic changes in the properties of the resulting compounds. Neither Merce-Vidal et al nor Filla et al provide any reasonable basis to conclude that making the substitutions and modifications to the compound disclosed by Merce-Vidal et al based on Filla et al would have similar activity.

Despite the foregoing, the Examiner alleged that this showing is not persuasive because none of the compounds referenced is drawn to modulators of 5-HT_6. Even though Applicants maintain that the foregoing is germane to the question at hand, they provided an example of two different compounds that can be associated with a "positional isomerism" for which US patents have been granted: one of them proposed as 5-HT_6 antagonist and the other proposed for treating intraocular pressure or glaucoma, which are not related to 5-HT_6 receptor. Such compounds are respectively:

- RN: 244122-12-1 US 6,100,291 granted on August 8, 200;



- RN: 137642-51-4 US 5,607,933 granted on April 3, 1997.



As complementary note, it is remarkable that 244122-12-1, which has a tryptamine-like structure (as Filla et al, a 3-aminocycloalkylindole structure (i.e. a tertiary amine), acts as 5-HT_6 antagonist whereas when the pyrrolidinalkyl moiety is moved to position 1 (137642-51-4), the compound is indicated for disorders not related to said receptor such as the reduction of intraocular pressure.

Nevertheless, the Examiner didn't found persuasive this argument either because although it is clear that the referenced compounds are known to have different activities, it is

not clear that the compounds also lack the same activity. Further, the Examiner points that the compounds differ in more respects than the present case and it would be impossible to ascertain the reason of the difference in activity.

Applicants agree that the fact that one positional isomer possesses affinity for a receptor X and other positional isomer binds to receptor Y does not prevent, in itself, that the first isomer shows affinity for the receptor Y as well. However, such a reasoning is merely speculative and therefore the skilled artisan would only readily understand from the referenced examples that positional isomers may show very different activities.

Thus, the skilled artisan considering Merce-Vidal et al in light of the prior art, could expect changing the $-(CH_2)_n-R^2$ moiety to position 1 to have dramatic changes in the properties of the resulting compounds.

In view of the foregoing, Applicants submit that the combined disclosures of Merce-Vidal et al taken with Filla et al fail to support a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Finally, Applicants request withdrawal of the objection to Claims 83 and 91 as being dependent upon a rejected base claim in view of the remarks above.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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